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A Randomized Controlled Trial of Platelet Activity Before and After Cessation of Clopidogrel Therapy in Patients With Stable Cardiovascular Disease

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Objectives The aim of this randomized placebo-controlled trial was to determine if withdrawing clopidogrel therapy leads to increased platelet activity compared with pre-treatment values in patients with stable coronary artery or peripheral arterial disease.

Background Reports of increased cardiovascular events after planned cessation of clopidogrel therapy have raised concerns over the possible existence of a rebound in platelet activity.

Methods In all, 171 patients receiving established aspirin therapy were randomly assigned to placebo or clopidogrel (75 mg daily) for 28 days. Blood samples were taken at pre-treatment baseline, on treatment just before discontinuation of study drug, and on days 7, 14, and 28 after discontinuation. The primary outcome measure was adenosine diphosphate (ADP)-stimulated platelet fibrinogen binding. Six secondary outcomes were assessed: ADP-stimulated platelet P-selectin, unstimulated platelet fibrinogen binding, and light transmission aggregometry with ADP 5 and 10 μmol/l recorded at maximum and at 6 min.

Results The ADP-stimulated platelet fibrinogen binding, P-selectin expression, and platelet aggregation were lower on treatment with clopidogrel compared with baseline ($p < 0.0001$), but returned to baseline levels by 7 days after discontinuation. Mixed model analyses excluding the on-treatment timepoint showed no overall differences between the clopidogrel and placebo groups ($p > 0.05$). Furthermore, there was no evidence of an interaction between platelet inhibition over time and treatment allocation.

Conclusions This trial found no evidence for rebound of platelet activity to above baseline after stopping clopidogrel in patients with stable coronary artery disease or peripheral arterial disease. (Is Cessation of Clopidogrel Therapy Associated With Rebound of Platelet Activity in Stable Vascular Disease Patients?; ISRCTN77887299/77887299)
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The thienopyridine derivative, clopidogrel, is an effective inhibitor of platelet activation and aggregation as a result of its selective and irreversible blockade of the $P2Y_{12}$ receptor (1). Clopidogrel monotherapy is recommended for patients with peripheral arterial disease (PAD), and a combination of aspirin and clopidogrel may be prescribed for patients "who are not at increased risk of bleeding and who are at high perceived cardiovascular risk" (2). Guidelines recommend the use of combination antiplatelet therapy with clopidogrel and aspirin for patients with acute coronary syndromes and for patients undergoing coronary artery stenting for 1 year (3–5). Recently, a number of large studies have highlighted increased morbidity and mortality after planned cessation of clopidogrel therapy in these patients (6–8).

It has been postulated that the increase in thrombotic events could be due to a rebound in platelet activity (9,10). However, in previous studies (11–13), platelet activity before commencing clopidogrel was not assessed, and therefore, it is unclear whether platelet activity after withdrawal

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Abbreviations and Acronyms

ADP = adenosine diphosphate

CAD = coronary artery disease

PAD = peripheral arterial disease

was any higher than pre-treatment levels. The implications of a possible rebound effect are clearly important (14,15), and we aimed to determine whether a course of clopidogrel therapy followed by withdrawal leads to increased platelet activity compared with pre-treatment values in patients with stable coronary artery disease (CAD) or PAD.

Methods

Patients. One hundred seventy-one patients were recruited between June 8, 2009, and May 30, 2012. Patients were identified from prospectively gathered databases and from cardiac and claudication clinics. Comorbidity and medications were documented. Ethical approval was obtained (NOSRES 08/S0801/087), and each patient gave written informed consent. The trial was registered (ISRCTN77887299), approved by Medicines and Healthcare Products Regulatory Agency (EudraCT 2007-007638-21), and conducted according to Good Clinical Practice.

This was a randomized, placebo-controlled, double-blind study. Inclusion and exclusion criteria are shown in Table 1. Patients were allocated to clopidogrel 75 mg daily (diluted with Lactose PhEur and encapsulated) or indistinguishable placebo capsules containing Lactose PhEur 540 mg (Tayside Pharmaceuticals, Dundee, Scotland) for 30 days according to a computer-generated minimization program to balance age, sex, and smoking status (16). All patients received appropriate risk factor treatment including statin and 75 mg aspirin daily throughout the study and were followed up for 28 days after cessation of clopidogrel/placebo. Participants were randomized just after the baseline blood sample and awaited instructions to confirm their blood profile was within safe limits (17) before commencing study medication.

Outcomes. The primary outcome measure was ADP-stimulated platelet fibrinogen binding, with 6 pre-specified secondary outcome measures: ADP-stimulated platelet P-selectin expression, unstimulated platelet fibrinogen binding, and ADP-stimulated platelet aggregation (at 2 concentrations: 5 and 10 μmol/l) recorded at both maximum and at 6 min.

Samples and assays. Blood samples were taken in the morning at: 1) baseline, 24 h before commencing clopidogrel or placebo; 2) on treatment, just before discontinuation of clopidogrel or placebo (day 28 ± 2), between 1 to 4 h after ingestion of drug; 3) 7 days after drug discontinuation; 4) 14 days after discontinuation; and 5) 28 days after discontinuation.

PLATELET ACTIVATION MARKERS. Platelet fibrinogen binding with and without stimulation with ADP (10 μmol/l) or thrombin receptor-activating-peptide (10 μmol/l), and platelet P-selectin (CD62P) expression with and without ADP (10 μmol/l), were assayed in diluted whole blood samples by flow cytometry (18); intra-assay coefficient of variation was <10%. Light transmission aggregometry was performed in platelet-rich plasma with ADP (Sigma-Aldrich, St. Louis, Missouri) 5 and 10 μmol/l and arachidonic acid (Alpha Laboratories, Hampshire, United Kingdom) 1.5 mmol/l (19). Von Willebrand factor antigen was measured in plasma by in-house enzyme-linked immunosorbent assay, as previously described (20), with an interassay coefficient of variation 9.0%.

Statistical analysis. Based on data from a previous trial (18), to detect a difference of 10 percentage units in ADP-induced fibrinogen binding with a standard deviation of 25 U, using a 1-sided *t* test, a sample size of 78 participants per group was required (assuming 80% power and a 5% significance level).

Descriptive results were produced for all outcomes, but statistical testing was only performed for the primary and secondary outcomes. The primary research question was addressed using a mixed model procedure, xt-mixed in Stata (21), using 7 models, 1 for each primary and secondary outcome measure, excluding the on-treatment timepoint but including baseline and 7, 14, and 28 days

Table 1 Inclusion and Exclusion Criteria

Inclusion criteria
Age 30–80 yrs
Coronary artery disease
Chronic stable angina
Canadian Cardiovascular Score 1 to 3 with prior angiographic evidence of >50% stenosis in at least 1 major coronary artery
Or
History of prior myocardial infarction
Preserved left ventricular systolic function
Or
Peripheral arterial disease
Stable intermittent claudication and ABPI <0.9
Receiving 75 mg aspirin and statin
Exclusion criteria
Age >80 yrs
Unable to give informed consent
Unstable symptoms over the preceding 3 months
Clinical symptoms of heart failure
Rest pain or ulceration
Known allergy or contraindications to clopidogrel (16)
Liver impairment: aspartate aminotransferase, alkaline phosphatase, or gamma-glutamyl transferase >3 times upper limit of normal
Platelet count $<140 \times 10^9$/l
Neutrophil count $<1.5 \times 10^9$/l
Abnormal renal function: creatinine >2 times upper limit of normal, on screening
Bleeding diathesis
Participation in another CTIMP in preceding 3 months
Currently taking
Antiplatelet or anticoagulant drugs other than aspirin
Omeprazole or esomeprazole

ABPI = ankle-brachial pressure index; CTIMP = clinical trial of an investigational medicinal product.

after treatment. An indicator of randomized group was included as an independent variable in each model. The effect of patient was treated as a random effect and results were adjusted for the minimization variables (age, sex, and smoking status) and diabetes mellitus. Timepoint was included as a panel variable, and interaction between time and randomized group was also included. Unstimulated fibrinogen binding was not normally distributed so it was log transformed before analysis.

For secondary analyses, baseline and on-treatment values for the clopidogrel group were compared using paired *t* tests (Wilcoxon test for unstimulated fibrinogen binding).

Results

One hundred seventy-one participants were recruited; 159 participants attended all visits and were included in the main analyses (Fig. 1). The clopidogrel and placebo groups were similar with respect to age, sex, smoking status, and medical history (Table 2). Compliance was good, with only 2 patients missing >2 capsules (placebo).

Effect of clopidogrel/placebo (pre-treatment versus on-treatment sample). In the clopidogrel group, the primary outcome (ADP-stimulated platelet fibrinogen binding) (Fig. 2) and all secondary outcomes, except

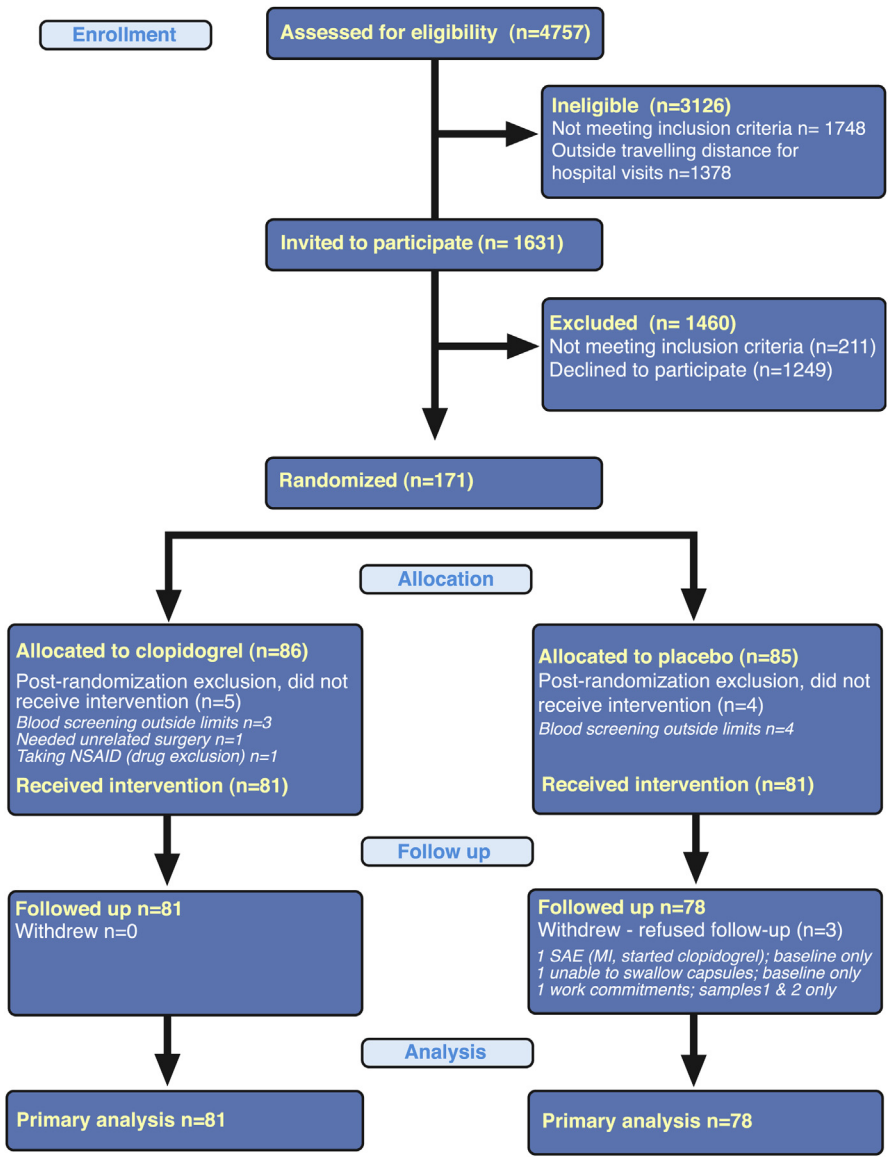

Figure 1 CONSORT Diagram of Flow of Participants

CONSORT = Consolidated Standards of Reporting Trials; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; SAE = serious adverse event(s).

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Table 2 Patient Demographics by Randomized Group

	Clopidogrel (n = 81)	Placebo (n = 81)
Sex		
Male	68 (84)	68 (84)
Female	13 (16)	13 (16)
Smoking status		
Nonsmoker	18 (22)	18 (22)
Current/ex-smoker	63 (78)	63 (78)
Diabetes mellitus	8 (10)	6 (7)
Peripheral arterial disease	23 (28)	13 (16)
Coronary artery disease	70 (86)	72 (89)
CAD initial presentation		
MI	44	49
Angina	26	23
Prior revascularization for CAD		
PCI	62	65
CABG	7	5
Hypertension	27 (33)	25 (31)
ACE inhibitors	57 (70)	56 (69)
Beta-blockers	52 (64)	58 (72)
Age, yrs	64.3 ± 8.0 [81]	65.2 ± 9.0 [81]
Body mass index, kg/m^2	29.7 ± 4.7 [81]	29.2 ± 4.0 [80]

Values are n (%), n, or mean ± SD [n].

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

unstimulated fibrinogen binding, were statistically significantly lower on treatment than at baseline ($p < 0.0001$) (Fig. 3, Tables 3 and 4). Of the other measures, only thrombin receptor-stimulating peptide–stimulated fibrinogen binding was reduced (Online Table 1). In the placebo group, platelet outcomes remained at levels similar to baseline.

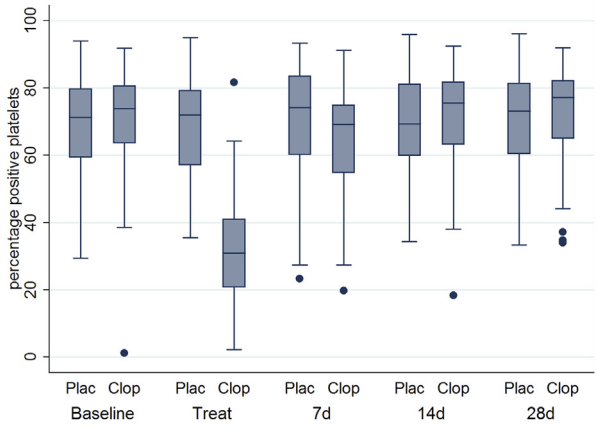

Figure 2 ADP-Stimulated Platelet Fibrinogen Binding in the Placebo and Clopidogrel Groups

Boxplots with bars indicate median, **boxes** represents 25th to 75th percentiles (interquartile range [IQR]), and **whiskers** indicate upper and lower limits, with outliers beyond 1.5 × IQR from the 25th to 75th percentiles. ADP = adenosine diphosphate 10 μmol/l; Baseline = pre-treatment sample; Clop = clopidogrel; Plac = placebo; Treat = on-treatment sample; 7d = 7 days after treatment cessation; 14d = 14 days after treatment cessation; 28d = 28 days after treatment cessation.

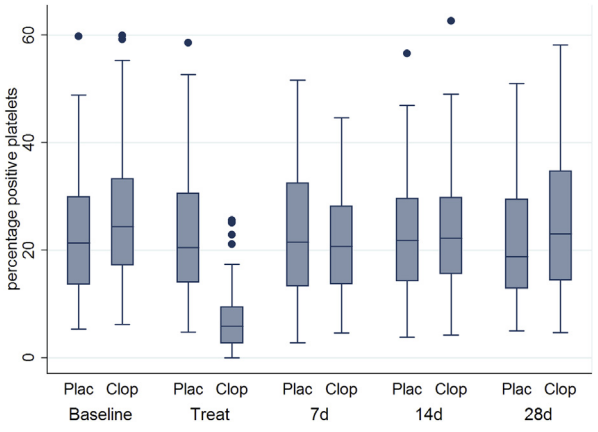

Figure 3 ADP-Stimulated Platelet P-Selectin Expression in the Placebo and Clopidogrel Groups

Boxplots with bars indicate median, **boxes** represents 25th to 75th percentiles (interquartile range [IQR]), and **whiskers** indicate upper and lower limits, with outliers beyond 1.5 × IQR from the 25th to 75th percentiles. Abbreviations as in Figure 2.

Effect of cessation. By 7 days, all outcomes had returned to baseline levels. Results for the clopidogrel and placebo groups remained similar at each of the post-treatment timepoints (Figs. 2 and 3, Tables 3 and 4). The mixed model analyses (Table 5) showed no statistically significant differences in the overall pattern of results between the clopidogrel and placebo groups for any of the primary or secondary outcome measures ($p > 0.05$). There was no evidence for a treatment-time interaction effect in any of the models, indicating that the results were stable over time.

Discussion

This study has shown no evidence of a rebound effect after cessation of short-term clopidogrel therapy in patients with stable CAD or PAD. Importantly, this is the first study to allow comparison of pre- and post-treatment activity for 1 month in stable patients and also to include a placebo group, while comprehensively assessing a range of markers of platelet activation and aggregation.

As expected, clopidogrel therapy was associated with a significant reduction in ADP-stimulated fibrinogen binding, P-selectin expression, and platelet aggregation. All platelet outcomes returned to baseline by 1 week after cessation of clopidogrel and remained stable at the 14- and 28-day timepoints. Importantly, there were no statistically significant differences overall between the clopidogrel and placebo groups after treatment.

A number of small studies showed apparent increases in platelet activity after planned cessation of clopidogrel in patients with diabetes mellitus (9) and/or stable CAD (11,12). Among patients stopping clopidogrel 12 months after stent insertion, Mylotte et al. (12) found a peak in light-transmission platelet aggregation at 1 month after cessation

Table 3 Results of Primary and Secondary Outcome Measures: Platelet Activation Markers by Flow Cytometry in Placebo and Clopidogrel Groups at Each Time Point

	Baseline		On Treatment		7 Days Post-Treatment		14 Days Post-Treatment		28 Days Post-Treatment	
	Clop	Placebo	Clop	Placebo	Clop	Placebo	Clop	Placebo	Clop	Placebo
ADP-stimulated fibrinogen binding, %	73.9 (63.6–80.6) [81]	71.3 (59.4–79.8) [81]	30.9* (20.8–41) [79]	72.1 (57.1–79.2) [78]	69.2 (54.8–74.9) [79]	74.1 (60.2–83.6) [77]	75.6 (63.2–81.8) [78]	69.4 (59.9–81.1) [77]	77.3 (65.0–82.2) [80]	73.2 (60.4–81.4) [77]
Unstimulated fibrinogen binding, %	1.31 (0.71–2.16) [81]	1.24 (0.75–1.97) [81]	1.24 (0.72–2.09) [79]	1.25 (0.62–2.25) [78]	1.46 (0.65–2.51) [79]	1.5 (0.68–2.45) [77]	1.51 (0.70–2.96) [79]	1.6 (0.75–2.77) [77]	1.48 (0.62–2.33) [80]	1.34 (0.82–2.65) [77]
ADP-stimulated platelet P-selectin, %	24.4 (17.2–33.3) [81]	21.4 (13.7–30.0) [80]	5.91* (2.72–9.51) [77]	20.5 (14.0–30.6) [77]	20.8 (13.7–28.2) [78]	21.5 (13.3–32.5) [76]	22.2 (15.6–29.8) [78]	21.8 (14.3–29.6) [77]	23.0 (14.4–34.7) [80]	18.8 (12.9–29.5) [77]

Values are median (interquartile range) [n]. *On-treatment versus baseline, paired *t* test $p < 0.0001$.
ADP = adenosine diphosphate; Clop = clopidogrel; IQR = interquartile range; max = maximum.

Table 4 Results of Secondary Outcome Measures: Light Transmission Aggregometry in Placebo and Clopidogrel Groups at Each Time Point

	Baseline		On Treatment		7 Days Post-Treatment		14 Days Post-Treatment		28 Days Post-Treatment	
	Clop	Placebo	Clop	Placebo	Clop	Placebo	Clop	Placebo	Clop	Placebo
ADP 5 μmol/l aggregation max, %	55.6 ± 10.9 [81]	53.1 ± 9.6 [81]	34.0* ± 11.0 [80]	52.1 ± 12.2 [77]	52.4 ± 9.9 [80]	53.4 ± 9.6 [77]	55.6 ± 10.1 [78]	53.8 ± 9.7 [77]	54.1 ± 9.1 [79]	53.3 ± 10.7 [77]
ADP 5 μmol/l aggregation 6 min, %	48.1 ± 13.4 [81]	45.0 ± 13.5 [81]	15.6* ± 12.1 [79]	44.4 ± 13.6 [77]	42.8 ± 11.7 [80]	45.7 ± 12.3 [77]	48.7 ± 12.2 [78]	45.8 ± 13.1 [77]	46.5 ± 11.0 [79]	45.2 ± 13.8 [77]
ADP 10 μmol/l aggregation max, %	64.1 ± 10.8 [81]	61.8 ± 9.1 [81]	42.7* ± 12.7 [80]	60.7 ± 12.4 [77]	60.8 ± 9.6 [80]	61.4 ± 9.6 [77]	62.5 ± 10.5 [78]	63.1 ± 11.1 [77]	62.3 ± 10.2 [79]	61.7 ± 11.0 [77]
ADP 10 μmol/l aggregation 6 min, %	60.3 ± 11.8 [81]	57.8 ± 11.1 [81]	25.7* ± 15.5 [79]	56.8 ± 13.0 [77]	55.4 ± 10.6 [80]	57.4 ± 11.2 [77]	59.6 ± 11.7 [78]	59.2 ± 12.0 [77]	59.1 ± 11.2 [79]	57.6 ± 12.7 [77]

Values are median ± SD [n]. *On-treatment versus baseline, paired *t* test $p < 0.0001$.
Abbreviations as in Table 3.

Table 5 Results of 7 Mixed Model Analyses Predicting Primary and Secondary Outcome Measures

Independent Variable	Focal Category	ADP-Platelet Fibrinogen Binding	Unstimulated Fibrinogen Binding	ADP-Platelet P-Selectin	ADP 10 μmol/l Aggregation Max	ADP 10 μmol/l Aggregation 6 Min	ADP 5 μmol/l Aggregation Max	ADP 5 μmol/l Aggregation 6 Min
Randomized group	Clopidogrel	−1.85 (−7.25 to 3.55)	−0.04 (−0.39 to 0.31)	0.13 (−3.64 to 3.91)	1.77 (−1.89 to 5.43)	1.01 (−3.08 to 5.09)	1.59 (−1.91 to 5.08)	1.09 (−3.23 to 5.42)
Time point	—	0.52 (−0.70 to 1.74)	0.02 (−0.06 to 0.09)	−0.51 (−1.08 to 0.06)	0.12 (−0.74 to 0.98)	0.12 (−0.81 to 1.05)	0.06 (−0.73 to 0.84)	0.02 (−0.87 to 0.91)
Group-time interaction	—	0.94 (−0.77 to 2.65)	0.02 (−0.09 to 0.13)	0.36 (−0.44 to 1.15)	−0.49 (−1.70 to 0.72)	−0.08 (−1.38 to 1.23)	−0.17 (−1.28 to 0.94)	0.12 (−1.13 to 1.37)
Age	—	0.07 (−0.13 to 0.26)	−0.003 (−0.02 to 0.01)	0.16 (−0.04 to 0.35)	0.05 (−0.08 to 0.17)	0.08 (−0.07 to 0.22)	0.07 (−0.06 to 0.19)	0.14 (−0.04 to 0.32)
Sex	Female	1.78 (−2.87 to 6.43)	0.01 (−0.30 to 0.31)	0.12 (−4.39 to 4.62)	5.05 (2.12 to 7.98)*	6.36 (2.88 to 9.84)*	6.08 (3.06 to 9.09)*	7.17 (2.95 to 11.40)*
Smoking status	Current/ ex-smoker	2.97 (−1.18 to 7.11)	0.36 (0.09 to 0.63)*	−1.00 (−5.02 to 3.02)	1.53 (−1.09 to 4.14)	1.94 (−1.17 to 5.04)	1.70 (−0.98 to 4.39)	2.25 (−1.51 to 6.02)
Diabetes mellitus	Yes	−0.71 (−6.61 to 5.18)	−0.29 (−0.68 to 0.10)	1.72 (−4.00 to 7.43)	1.37 (−2.34 to 5.08)	1.71 (−2.70 to 6.13)	1.24 (−2.58 to 5.06)	1.86 (−3.50 to 7.21)

Numbers in the table indicate the model coefficients with 95% confidence intervals from the 7 mixed models (see Statistics section). Only data from baseline and 7, 14, and 28 days after treatment were included. Independent variables: randomized group; time point (panel variable), age, sex, smoking status, diabetes mellitus, and interaction between time and randomized group. The effect of patient was treated as a random effect. *$p < 0.05$ for variables that had a statistically significant effect on the model.
Abbreviations as in Table 3.

of treatment compared with 3 months, whereas a study by Diehl et al. (11) found increased whole blood aggregation at 2 and 6 weeks compared with 17 weeks. However, none of these studies included a pre-treatment baseline.

Consistent with our findings, in crossover studies of $P2Y_{12}$ inhibitors for stable CAD patients (22) or stable CAD with diabetes (23), when pre- and post-treatment platelet aggregation were assessed there was no significant difference from baseline at 7 to 10 days after withdrawal. Similarly, a small placebo-controlled study involving healthy subjects observed no increases in a comprehensive range of platelet tests after discontinuation of clopidogrel compared with baseline (24).

In stable CAD patients, 6 to 12 months after drug-eluting stent insertion, ADP aggregation showed recovery up to 1 week after discontinuation of clopidogrel, but values remained steady out to 4 weeks (13,25). In a larger study of 200 stable CAD patients 12 months after stenting, whole blood aggregation reached a plateau by 10 days after stopping, and remained stable at 45 and 90 days (26).

Study limitations. The main limitation of the present study was that patients received clopidogrel for only 1 month, so chronic changes may have been missed. It has been postulated that long-term clopidogrel therapy could lead to increased sensitivity of the $P2Y_{12}$ receptor through increased coupling or expression (27). However, clinical events have been shown to occur more frequently in patients who discontinued clopidogrel within 1 month of commencement (28). Furthermore, given the half-life of platelets and the irreversible inhibition by clopidogrel, it is highly unlikely that we have missed an earlier or a later rebound effect. It is important to note that all participants had stable CAD or PAD and were pre-dominantly male and smokers, with a minority of diabetic patients. The results are not generalizable to the whole population and are not of relevance to patients who have sustained a recent acute thrombotic event.

Conclusions

The findings of this study provide reassurance that there is no evidence of a platelet rebound effect when clopidogrel is withdrawn in patients with stable CAD or PAD.

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Key Words: clopidogrel ■ platelets ■ rebound.

APPENDIX

For a supplemental table, please see the online version of this article.